

Can mirabegron facilitate ureteral access sheath placement during flexible ureterorenoscopy?

Mirabegron and ureteral access sheath placement

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Abstract

Aim: In this study, we aimed to demonstrate the effect of mirabegron on ureteral access sheath (UAS) placement during flexible ureterorenoscopy (f-URS).

Material and Methods: The study enrolled 96 patients with renal stones who underwent f-URS between October 2019 and March 2020. The patients were divided into 2 groups. Mirabegron treatment was administered 2 weeks before f-URS in Group 1 (n = 41), and no mirabegron treatment was given in Group 2 (n = 55). All operations were performed by a single surgeon (MK). Demographic characteristics were recorded for each patient, including age, body weight, height, body mass index (BMI), stone characteristics, and perioperative data, including operation-fluoroscopy durations, stone-free rates, complications, and surgery success rates. Group data were compared, and p-values less than 0.05 were considered statistically significant.

Results: No significant difference was detected between the groups in terms of age, sex, body mass index, number and size of stones, side of stones, density of stones, and renal hydronephrosis level. UAS placement in Group 1 was found to be statistically significant at the first attempt (without using a semi-rigid ureteroscope or balloon dilatation) compared with Group 2 (p=0.001).

Discussion: The use of mirabegron may facilitate UAS placement during f-URS with less operation time and fewer complications.

Keywords

Flexible ureterorenoscopy; Mirabegron; Retrograde intrarenal surgery; Ureteral access sheath

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Introduction

Flexible ureterorenoscopy (f-URS) is widely used for the detection and treatment of renal stones and pathologies of the upper urinary tract. During this procedure, a ureteral access sheath (UAS) is generally inserted into the ureter to facilitate the passage of the flexible ureterorenoscope. However, in some cases, the UAS cannot be advanced from the ureter orifice into the ureter, and the operation is cancelled until the next session by inserting a double-j stent [1, 2].

Mirabegron stimulates the bladder's adrenergic beta-3 receptors and is used in the treatment of overactive bladder. [3] It relaxes the bladder's smooth muscle through beta-3 agonistic effects and thus has a wide range of uses in other diseases, such as distal ureteral stones. Mirabegron has been shown to facilitate stone expulsion, especially in cases of distal ureteral stones less than 0.5 cm [4]. In this study, we aimed to investigate whether mirabegron can facilitate the passage of UAS in f-URS procedures.

Material and Methods

The study was performed in an observational prospective non-randomized manner. The ethical approval for this study was obtained from the Erciyes University Institutional Review Board (IRB Decision no: 2019/706 Decision date: 09.10.2019). The study included patients with renal stones who were scheduled for f-URS between October 2019 and March 2020 in the department of urology of Kayseri City Hospital. Informed consent was obtained from all individual participants included in the study.

The patients were divided into 2 groups. If we conducted the study in terms of $\alpha=0.05$ and the power as 0.8, the sample size of the study was determined as 96. The number of patients in Group 1 was 41, and the number of patients in Group 2 was 55. In Group 1, seven patients were excluded for refusing medical therapy, and one patient was excluded due to a previous stenosis operation. Two patients in Group 2 were excluded due to alpha-blocker and calcium channel blocker medication. As a result, 33 patients in Group 1 and 53 in Group 2 were included in statistical analysis. Mirabegron treatment (50 mg once daily) was administered 2 weeks before f-URS in Group 1 ($n = 41$), and no mirabegron treatment was given in Group 2 ($n = 55$). All of the patients were prescribed non-steroidal anti-inflammatory medications for pain relief during this period. The patients' complete blood count, biochemistry, urinalysis, urine culture, and abdominal computed tomography were examined. Demographic characteristics were recorded for each patient including age, body weight, height, body mass index (BMI), stone characteristics, and perioperative data including operation-fluoroscopy durations, stone-free rates, complications, and surgery success rates.

Patients were excluded from the study if they had previous operations for lower urinary tract pathology, ureteral stones, bilateral renal stones, advanced prostate enlargement, double-j stents, or any other medical treatments that could cause dilatation of the ureter and did not accept medication (alpha-blockers, calcium canal blockers, etc.). All operations were performed by a single surgeon (MK) using the same flexible ureterorenoscope (7.5fr Storz Flex-X2, Tuttlingen, Germany) and

the same UAS (9.5fr-11.5fr, 35 cm Cook, Blooming, USA). We did not have a special device for detection of ease in insertion of UAS, so the ease in insertion of UAS during the procedures was noted by MK's subjective sense. MK is an experienced urologist in f-URS procedures with over 1000 cases.

A 0.038-inch hydrophilic guidewire (ZIPwire Nitinol Hydrophilic Guidewire, Boston Scientific, Marlborough, MA, USA) was inserted into the ureter through a semi-rigid ureterorenoscope (6.5/8.5 fr, Richard Wolf, Illinois, USA), and UAS placement was performed over the guidewire. As a routine of our department, no extra safety guide wire was used in fURS. We didn't enter into the ureter with a semi-rigid ureterorenoscope before the insertion of UAS. In cases of failure, mechanical dilatation was attempted after insertion of a semi-rigid ureterorenoscope. If we failed after mechanical dilatation, ureteral balloon dilatation was performed. A double-j stent was placed into the ureter, and the operation was postponed until the next session (4 weeks) for patients where the ureteral balloon failed. Complications were evaluated according to the modified Clavien system [5]. Complications of Grade 1, 2, or 3 were considered minor, while Grade 4 or 5 complications were considered major.

Statistical analyses

The program IBM software released in 2013 (IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.) was used for statistical analysis. The distribution characteristics of numerical data were determined according to the Shapiro-Wilk test and histogram graphs. Numerical data showing normal distribution were expressed as the mean \pm standard deviation, non-normally distributed numerical data were expressed as the median (1st-3rd quartile), and categorical data were expressed as a percentage (%). Categorical data were compared with the Chi-squared test (Pearson or Fisher Exact test). The Levene's test and an independent-samples t-test were used to analyze the numerical data from the independent groups with a normal distribution, and the Mann Whitney-U test was used to analyze data showing a non-normal distribution. A p-value of less than 0.05 was considered statistically significant.

Results

The demographic data and preoperative characteristics of the patients are summarized in Table 1. The mean age of the patients was 53.17 (± 13.96) years, the BMI was 27.72 (± 3.7), the median number of stones was 1.0 (1.0-2.0), and the median stone size was 16.0 mm (13.0-22.0). No significant difference was detected between the groups in terms of age, sex, BMI, number and size of stones, side of stones, density of stones, and renal hydronephrosis level ($p>0.05$).

UAS placement in Group 1 was significantly successful at the first attempt (without using a semi-rigid ureteroscopy or balloon dilatation) ($p=0.001$). Operations were postponed for 4 weeks by implanting a double-j stent in 4 patients in Group 1 and 7 patients in Group 2. Two minor complications (bleeding and urinary tract infection) and 3 minor complications (urinary tract infection ($n = 1$), ureteral mucosal erosion ($n = 2$)) were recorded in Groups 1 and 2, respectively. Three major complications (perforation ($n = 1$) and steinstrasse ($n = 2$)) were observed in Group 2, but no major complication occurred in Group 1. There were no side effects observed in the mirabegron group.

Operative and postoperative characteristics are summarized in Table 2.

Table 1. Demographics and pre-operative patient characteristics

		Group 1 (n=33)	Group 2 (n=53)
Age, years		51.67±16.05	54.08±12.68
Gender (n)	Male	23	27
	Female	10	28
BMI (kg/m2)		26.85±2.83	28.23±4.11
Total stone burden, mm		15.0 (12.0-24.5)	16.0 (13.0-22.0)
Stone number		1.0 (1.0-2.0)	1.0 (1.0-2.0)
Laterality (n)	Right kidney	11	23
	Left kidney	22	30
Renal stone density (HU)		910.0 (821.5- 985.0)	903.0 (812.0-976.0)
Hydronephrosis (n)	None	11	19
	Mild	16	24
	Moderate or severe	6	10

Table 2. Operative and postoperative characteristics

UAS placement in the first attempt n, (%)	Yes	No	p
Group 1	22(66.6%)	11(33.3%)	0.001
Group 2	17 (32%)	36 (67.9%)	
UAS placement after semi-rigid ureteroscopy or ureteral balloon dilatation n,(%)	Yes	No	p
Group 1	29(87.8%)	4(12.%)	0.934
Group 2	48(90.5%)	5(9.4%)	
Postoperative d-j stent placement n,(%)	Yes	No	p
Group 1	32(96.9%)	1(3%)	0.384
Group 2	51(96.2%)	2(3.7%)	
Stone free rate (First month) n, (%)	Stone free	Residual stone	p
Group 1	30(90.9%)	3(9%)	0.333
Group 2	48(90.5%)	5(9.4%)	
Fluoroscopy performed n, (%)	Yes	No	p
Group 1	2(6%)	31(93.9%)	-
Group 2	0	53(100%)	
Operation duration (minutes)	Group 1	Group 2	p
	42.62±12.54	50.79±19.96	0.04
Complications (n)	Group 1	Group 2	
Bleeding	1	-	
Urinary tract infection	1	1	
Ureteral mucosal erosion	-	2	
Perforation	-	1	
Steinstrasse	-	2	

UAS: ureteral access sheath

Discussion

The advantages of using a UAS during f-URS are the provision of fluid drainage, reduced renal calyceal pressure, reduced risk of sepsis, and enabling repeated access to the ureter and collecting system for a flexible ureteroscope [6, 7].

It has also been shown that the use of UAS prolongs the life of the flexible ureterorenoscope [8]. The service life of the flexible ureterorenoscope is important in terms of operating costs, especially in underdeveloped and developing countries. Complications that may occur during UAS insertion range from ureteral mucosal injuries to avulsion [9]. In addition, it has been shown in animal models that the use of UAS depresses the ureteral wall and disrupts ureteral blood flow, which may later result in ischemia and ureteral stenosis [10].

Mirabegron is a drug that is used in patients with overactive bladder and acts by stimulating selective beta-3 receptors. Mirabegron increases the capacity of the bladder by relaxing mechanism and affecting its filling function without affecting its contractility or flow rates [10,11]. Animal experiments have also demonstrated dilatation of the ureter and a decrease in ureteral intraluminal pressure with the use of mirabegron [12]. In addition, it has been reported to be an effective and safe medical expulsive treatment agent for the reduction of distal ureteral stones with a low rate of side effects [4, 14]. Mirabegron reduces the disturbing symptoms related to stents by dilatation of the ureter and decreasing intraluminal pressure [15]. These effects led to the idea that the use of mirabegron during UAS placement might provide convenience to the surgeon. It was also concluded that mirabegron makes it easier to access the ureter with semi-rigid ureteroscopy. [16]. The operation time between the two groups was approximately 8 minutes and it was statistically in favor of the mirabegron group. We think that this might be attributable to the success in the insertion of UAS in the first attempt.

The results showed that UAS implantation was more successful in patients who received mirabegron (56.4% vs. 43.6%, p= 0.001). However, this significant difference disappeared after the use of a semirigid ureteroscope or balloon dilatation (87.9% vs. 87.3%, p=0.934). This suggests that mirabegron facilitates UAS placement, but this effect can also be achieved if routine semi-rigid ureteroscopy is performed before the procedure. Therefore, the use of preoperative mirabegron alone does not seem to make sense to facilitate UAS passage. However, the duration of operation was significantly shorter in Group 1 than in Group 2, which may be related to the implementation of UAS in the first attempt (p = 0.04).

Bayar et al. found that the rate of access to the ureter with semi-rigid ureteroscopy was higher in patients who received tamsulosin and mirabegron arm, and they also required a balloon dilatation less often. This conclusion was parallel to the fact that UAS placement was more successful in the group receiving mirabegron [16]. In that study, 81% of ureter access was provided by a semi-rigid ureteroscope, and 56.4% of UAS placements were successful in the first attempt, even in the mirabegron group. We think that this difference may be attributable to the diameters of the ureteroscope (6/7.5-fr) and the UAS (9.5fr-11.5fr) that we used in our study.

In addition, Bayar et al. did not find a significant difference in terms of operation time between the control group and other groups. This may be explained by the immediate termination of more operations without stone disintegration due to worse access rates in the control group. However, we found that the operation time was shorter in the group using mirabegron.

The UAS passage was similar in both groups after semi-rigid ureteroscopy, so there was no early termination of the operation. This condition shows that the shortening of the operation time is related to the mirabegron.

Kaler et al. developed a device for measuring the power applied to the ureters of porcines during placement of UAS. They concluded that major ureteral injury can routinely be prevented if the UAS pushing force was <4.84N and occurred when forces were above 8.1 N. By this conclusion, they found an objective threshold value for pushing force of urologists during insertion of UAS. However, due to not having this newly developed device in our department, the ease of applying UAS to ureters was subjectively recorded by MK. On the other hand, to our knowledge, in the literature, there have been no studies on using this device in humans. [17]

Traxer et al. reported that serious complications related to UAS were significantly less common with preoperative double-j stenting. However, in this study, routine preoperative double-j stent use was not recommended because it causes uncomfortable symptoms in the urinary system and is not cost-effective [9]. Furthermore, routine stenting before f-URS procedures is not preferred by our center to avoid complications or failure.

Patients who did not receive mirabegron experienced complications during UAS placement in our study, such as mucosal erosion and perforation. Although mirabegron is thought to have a protective effect against complications, multi-center studies with a larger number of patients are required to make successful conclusions about this issue and increase the impact of the results. The small number of patients, single-center design and non-randomized manner are the main limitations of our study. Due to limitations in healthcare insurance of our country, it is really hard to conduct a study focusing on a molecule out of indication like our trial. We think that the other limitation might be not having a special device for detection of ease in insertion of UAS, so the ease in insertion of UAS during the procedures was noted by MK's subjective sense.

Conclusion

The preoperative use of mirabegron facilitates UAS placement, shortens the operation time, and may be protective against complications that may occur during UAS passage.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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